Remarks

Applicants note with appreciation the Examiner's withdrawal of the finality of the previous Office Action pursuant to the Applicants' Request for Continued Examination under 37 C.F.R. §1.114.

Claim 51 has been rejected under 35 U.S.C. §112, first paragraph, and §103. The Applicants have canceled Claim 51, thereby rendering the rejections moot. Claim 3 has been amended to incorporate the subject matter of Claim 6. Claim 6 has been canceled.

Rejections Under 35 U.S.C. §103

Claims 3-9, 25 and 50 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Carter in view of Hori and Presta.

Applicants respectfully submit that nothing in Hori describes the recombinant construction of heterodimeric molecules comprising α and β chains. In fact, Hori makes reference to integrins only once in the specification. (See Hori, Column 5, line 60). In particular, Hori teaches a **fused cell wherein the heavy and light chains are merely contained within the cell. Hence, the chains are not fused together**. The Examiner's attention is invited to Fig. 3 of Hori, wherein Hori articulates that one cell is constructed with a heavy chain, and a second cell is transformed with a light chain, and a desired hybrid cell is then formed by fusing the two separate cells together. The fused cell produces two separate antibodies, which are not fused together. (Hori, column 14, lines 16-24). Applicants respectfully submit that construction of a fused cell having heavy and light chains contained therein is vastly different from Applicants' claimed heterodimeric integrin molecule which has a heavy and light chain fused together.

Applicants' claimed molecule has heavy and light chains associated through disulfide bonds (e.g., a covalent bond between 2 sulfur atoms), and α and β units of integrin which are

non-covalently associated. (e.g. electrostatic or hydrogen bonds). Applicants respectfully submit that nothing in Hori teaches such a molecule. Furthermore, Carter describes prevention of disulfide bond formation by stating that "to ease chemical coupling of antibody fragments, Drennan *Science* 229: 81(1985) describe a procedure, wherein intact antibodies are protolytically cleaved to generate $f(ad)_2$ fragments. These fragments are reduced in the presence of dithiols and prevent intramolecular disulfide bond formation." Thus, Carter teaches prevention of intramolecular disulfide bond formation. In sharp contrast, Applicants' Claim 3 recites that the heavy chain of the immunoglobulin is bound to another heavy chain of immunoglobulin via disulfide linkage.

Applicants respectfully submit that even if the shortcomings of Hori, concerning construction of heterodimeric integrin molecules, could be overcome by those skilled in the art, there are no teachings or suggestions providing motivation to combine the process described in Carter with known integrin molecules to construct Applicants' claimed molecules. Moreover, nothing suggests a likelihood of success in constructing Applicants' claimed chimeric protein heterodimer complex using the process described in Carter.

Carter does not disclose construction of an integrin molecule. Carter discloses an adhesin molecule having a specific adhesive polymer sequence. Specifically, column 11, lines 7-12 of Carter state that "structurally, the immunoadhesins comprise a fusion of the adhesin amino acid sequence with the desired binding specificity, which is other than the antigen recognition and binding site." Not one exemplary immunoadhesin disclosed in Carter suggests an immunoadhesin containing an integrin. (Carter, Column 4, lines 13-35.)

Applicants respectfully submit that Carter describes a "protuberance-into-cavity" strategy, which serves to engineer an interface between a first and second polypeptide for hetero-

oligomerization. The Examiner's attention is invited to Carter at column 5, lines 41-58, which describes the protuberance-into-cavity procedure when it states:

> "Protuberances" are constructed by replacing small amino acid side chains from the interface of the first polypeptide with larger side chains (e.g. tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the protuberances are optionally created on the interface of the second polypeptide by replacing large amino acid side chains with smaller ones (e.g. alanine or threonine). Where a suitably positioned and dimensioned protuberance or cavity exists at the interface of either the first or second polypeptide, it is only necessary to engineer a corresponding cavity or protuberance, respectively, at the adjacent interface.
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> **Accordingly, the invention can be said to relate to a method of preparing a heteromultimer comprising a first polypeptide and a second polypeptide which meet at an interface, wherein the first polypeptide has a protuberance at the interface thereof which is positionable in a cavity at the interface of the second polypeptide.**

Carter uses "protuberances," constructed by replacing a small amino acid side chain from the interface of a first polypeptide with a larger side chain that is positionable into a cavity at the interface of a second polypeptide for the construction of the hetero-multimer. Using a protuberance-into-cavity methodology to create an immunoglobulin-integrin complex affects binding affinity, structural conformation, and a number of other features that can affect the function of Applicants' claimed chimeric protein heterodimer complex. With this background, the disclosure of Carter teaches away from combining the molecules described in Hori to construct a heterodimeric integrin molecule having α and β chains with 2 heavy Ig chains that are stably associated through a disulfide bond.

At best, using a "proturbence" methodology to create the Applicants' claimed complex would have only been "obvious to try," which has been strictly prohibited for many years. Similarly, Carter fails to provide any teaching or suggestion that the "proturbence" methodology could be used to construct Applicants' claimed complex. This is especially true in light of the

fact that, at the time this Application was filed (1998). Isolating and preparing a functional heterodimeric integrin molecule was extremely difficult due to an integrin molecule's non-covalent association between the α and β chain.

One skilled in the art, after reviewing Carter, would be led away from using a heterodimeric integrin molecule to construct an integrin immunoglobulin complex because Carter teaches a "protuberated" construction methodology which could affect the function of Applicants' claimed complex. Applicants respectfully submit that there is no suggestion that a heterodimeric integrin molecule could be constructed from the "protuberated" methodology of Carter. Nothing indicates that "protuberated" heterodimeric integrin molecules would properly function when fused to an Ig constant region. Moreover, as is well known in the art, the *Arg Gly Asp* (RGD) sequence of the ligand protein is important to ensure proper binding between an integrin and the ligand protein. Therefore, one skilled in the art would readily understand that introduction of a protuberance or cavity into an integrin could alter the integrin's ability to bind to the RGD sequence of the ligand protein.

Applicants claim a chimeric heterodimer protein comprising the α chain of an integrin and the heavy chain of an immunoglobulin and a ß chain of the integrin and the heavy chain of an immunoglobulin bound to one another by a disulfide bond between two heavy chains. Applicants respectfully submit that Carter, in combination with both Hori and Presta, fails to teach or suggest a heterodimeric integrin complex capable of associating the heavy chain of an immunoglobulin molecules, and the subsequent interaction of an "integrin immunoglobulin complex" with another "integrin immunoglobulin complex" to form a stable chimeric protein heterodimeric complex.

Applicants submit that nowhere on this record is there factual evidence showing either the motivation or the desire to utilize the "protuberance method" described in Carter to create a chimeric heterodimer integrin-immunoglobulin complex. Applicants submit that no evidence is provided illustrating that the technique described in Carter would be effective to create Applicants' claimed molecules.

Turning to Presta, the Applicants respectfully submit that Carter teaches away from the use of cysteines to mediate formation of a disulfide bond between the two heavy chains as described in Presta. Specifically, Carter states in column 13, line 55 that "the preferred import residue is not cysteine." Consequently, Applicants respectfully submit that this teaching is in direct contrast with Presta. Furthermore, Applicants respectfully submit that Presta teach **a trimetric structure**, which is vastly different from the Applicants' dimeric structure bound through a disulfide bond.

Applicants respectfully submit that the prior art fails to describe parameters critical to make a chimeric heterodimer integrin-immunoglobulin complex. There is no teaching or suggestion that Applicants' chimeric protein heterodimer protein can be created and/or maintain its binding affinity, by the using the "protuberance-into-cavity method" described in Carter.

As noted above, the Applicants have amended Claim 3 to include the subject matter of Claim 6. Accordingly, Claim 3 now recites that the chimeric protein heterodimer is restricted such that the integrin has two specific types of a combination of the α chain and β chain. By virtue of this specific combination of the α chain and β chain of integrin, the protein was first utilized as a platelet substitute. In particular, the Applicants first discovered that the protein may be used as a platelet substitute when the protein has the $\alpha 4$ and $\beta 1$ chains of integrain. This is described on page 16 of the Specification and in Examples 21 and 22. As for the protein having

$\alpha 2$ and $\beta 1$ chains of integrin, the Applicants discovered that this protein firmly binds to fibronectin, which is one of the extra cellular matrices. It therefore may be used as a platelet substitute as described in Example 9.

The Applicants respectfully submit that all of the prior art, whether taken individually or collectively, fails to teach or suggest the specific combination as set forth above, much less the utilization as a platelet substitute. Withdrawal of the rejection of Claims 3, 7-9, 25 and 50 under 35 U.S.C. §103(a) is respectfully requested.

In view of the foregoing, Applicants respectfully submit that the Application is now in condition for allowance, which is respectfully requested.

Respectfully submitted,

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